

Inconspicuous offender

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Valorization

Social and clinical relevance

The metabolic syndrome and cancer are among the top ten causes of deaths in upper middle-income and high-income countries to date placing high socioeconomic burdens on the developed world making them top world health concerns. NAFLD is the hepatic component of the metabolic syndrome. Currently, the prevalence of NAFLD is estimated to be 25% world-wide, predominantly in the West, with NASH making up 5% of the world population (1,2). Similarly, cancer is among diseases with the highest prevalence worldwide tallying 18 million new cases in 2018 alone (3). Clinicians face major challenges in diagnosing and treating NASH as early non-invasive testing is unavailable and the exact underlying mechanisms triggering hepatic inflammation are still largely unknown making liver transplantation the only effective treatment for advanced liver disorders stemming from NASH (4). Because of this, there is currently an enormous demand for novel more effective early non-invasive diagnostic and therapeutic tools for NASH. Also, cancer therapy suffers from major therapy-limiting factors such as the occurrence of therapy resistance, a persisting issue despite significant advances of (neo-)adjuvant chemotherapy and radiotherapy treatment protocols. Although these improvements have undoubtedly led to improved short-term cancer outcomes and reduced tumor burden, long-term survival and tumor eradication remain disappointing even though major progress in understanding of the molecular basis of treatment response has been acquired in recent years. In order to improve long-term outcomes, it is important to establish complementary intervention strategies that sensitize tumors to current therapies to increase the therapeutic ratio. As previously discussed in this thesis, there are striking similarities between metabolic derangements in cancer and diseases related to the metabolic syndrome e.g. atherosclerosis and NASH (5). Subject of this thesis in particular is the similarity of broad involvement of oxLDL in the pathologies of NASH and cancer. While oxLDL is long known to be a driver of disease particularly in metabolic diseases such as NASH, atherosclerosis as well as cancer, the mechanisms through which it does so remains poorly understood. By further exploring the role of oxLDL and related components in the pathophysiology of these metabolic diseases this thesis showcases the therapeutic potential of a non-invasive method of counteracting the detrimental oxLDL-induced effects through use of specific anti-oxLDL antibody strategies. Successful translation and implementation of these findings in the future into the clinic would potentially lead to improvement of quality of life for NASH and cancer patients and reduction of treatment cost.

Appendices

Novelty of the concept

In this thesis we investigated the mechanism through which oxLDL contributes to inflammation in NASH and the potential of oxLDL targeting in this setting. Hence this thesis provides new mechanistic insights of direct effect of oxLDL and the potential of directly targeting oxLDL in the context of NASH. Furthermore, while oxLDL has been extensively studied for its effect on cancer development and progression there has been no attempts to ascertain the benefits of targeting oxLDL directly in the context of cancer and little to no research on the effect of oxLDL on cancer therapy (3). This thesis expanded on the prospect of targeting oxLDL directly and suggests that this approach may be promising for future consideration. Finally, in recent years many studies have suggested that the future of therapy should be developed in the form of personalized treatment. This thesis further demonstrates the need for this consideration and that sex be a strong determining factor for this based on the duality of response to 27HC in men and women. In addition, this thesis also suggests a novel mechanism where differences ER receptor expression between men and women may possibly be key to explaining the differences in response to treatment between men and women.

Future perspectives and potential application

The studies described in this thesis facilitate the clinical translation of using oxLDL antibodies in NASH and cancer treatment. The fact that antibodies against oxLDL are naturally present in the human body makes them particularly attractive targets for intervention. And as there are already existing vaccines and new ones being developed to induce immunity against pneumococci infection which do not lead to any side effects, it further enables acceleration of the process of repurposing this vaccine for use in NASH and cancer clinical trials to target oxLDL. In the meantime, before this point of transition is reached, research is currently ongoing to further strengthen the basis of this approach. In particular the effectiveness of immunization in restoring treatment sensitivity *in vivo* will be determined. Additionally, the mechanism through which ER receptor expression is thought to result in variances of response between men and women still needs to be fleshed out and the effect of this verified across other diseases that show clear disparities between the sexes. This will facilitate future endeavors down the road to personalized treatment but also help with understanding mechanism of diseases that show discrepancies in pathophysiology between men and women.

Appendices

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